## Appendix 8 – meta-analysis of TCS versus TCI – cutaneous adverse events

## 1) Skin thinning

|  | Corticosteroid | 1(105) | Calcineurin innibito | r (TCI) |  | RISK RAUO           |  | RISK RAUO           |     |
|--|----------------|--------|----------------------|---------|--|---------------------|--|---------------------|-----|
| Study or Subgroup  | Events         | Total  | Events               | Total   | Weight                                 | M-H, Random, 95% CI |  | M-H, Random, 95% CI |     |
| Luger 2004 (1)   | 3              | 330    | 0                    | 328     | 26.5%                                  | 6.96 [0.36, 134.17] |  | -                   |     |
| Mandelin 2010 (2)  | 2              | 40     | 0                    | 40      | 25.7%                                  | 5.00 [0.25, 100.97] |  | -                   |     |
| Reitamo 2005 (3)   | 2              | 485    | 0                    | 487     | 25.2%                                  | 5.02 [0.24, 104.30] |  | -                   |     |
| Sigurgeirsson 2015 (4)   | 1              | 1213   | 0                    | 1205    | 22.7%                                  | 2.98 [0.12, 73.08]  |  | -                   |     |
| Total (95% CI)   |                | 2068   |                      | 2060    | 100.0%                                 | 4.86 [1.06, 22.28]  |  |                     |     |
| Total events   | 8              |        | 0                    |         |  |                     |  |                     |     |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.15, df = 3 (P = 0.99); i = 0% |                |        |                      |         |  |                     |  |                     | 100 |
| Test for overall effect: Z=  |                |        |                      |         | ore events with TCI More events with 1 |                     |  |                     |     |

2) Skin burning

|                                     | Corticosteroid                 | (TCS)       | Calcineurin inhibito       | r (TCI)  |        | Risk Ratio          | Risk Ratio          |
|-------------------------------------|--------------------------------|-------------|----------------------------|--|--------|---------------------|---------------------|
| Study or Subgroup                   | Events                         | Total       | Events                     | Total  | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Doss 2009 (5)                       | 9                              | 279         | 47                         | 287  | 9.1%   | 0.20 [0.10, 0.39]   |                     |
| Doss 2010 (6)                       | 6                              | 239         | 18                         | 237  | 6.4%   | 0.33 [0.13, 0.82]   |                     |
| Hofman 2006 (7)                     | 2                              | 124         | 10                         | 133  | 2.9%   | 0.21 [0.05, 0.96]   |                     |
| Luger 2001 (8)                      | 4                              | 42          | 22                         | 45   | 5.8%   | 0.19 [0.07, 0.52]   | <del></del>         |
| Luger 2004 (1)                      | 36                             | 330         | 85                         | 328  | 15.6%  | 0.42 [0.29, 0.60]   |                     |
| Reitamo 2002(I) (9)                 | 24                             | 186         | 113                        | 191  | 14.9%  | 0.22 [0.15, 0.32]   |                     |
| Reitamo 2002(II) (10)               | 13                             | 185         | 38                         | 186  | 10.7%  | 0.34 [0.19, 0.62]   |                     |
| Reitamo 2004 (11)                   | 30                             | 207         | 50                         | 210  | 14.5%  | 0.61 [0.40, 0.92]   |                     |
| Reitamo 2005 (3)                    | 67                             | 485         | 255                        | 487  | 18.4%  | 0.26 [0.21, 0.33]   | -                   |
| Sikder 2005 (12)                    | 1                              | 15          | 7                          | 15   | 1.8%   | 0.14 [0.02, 1.02]   |                     |
| Total (95% CI)                      |                                | 2092        |                            | 2119   | 100.0% | 0.31 [0.23, 0.40]   | •                   |
| Total events                        | 192                            |             | 645                        |  |        |                     |                     |
| Heterogeneity: Tau <sup>2</sup> = 0 | 0.09; Chi <sup>2</sup> = 21.66 | , df = 9 (F | $P = 0.01$ ); $I^2 = 58\%$ |  |        |                     |                     |
| Test for overall effect: Z          |                                |             |                            | 0.01 0.1 1 10 100<br>More events with TCI More events with TCS |        |                     |                     |

| 3) | Pruritus |
|----|----------|

|   | Corticosteroid                    | I (TCS)   | Calcineurin inhibit          | tor (TCI) |        | Risk Ratio          | Risk Ratio          |
|---|-----------------------------------|-----------|------------------------------|-----------|--------|---------------------|---------------------|
| Study or Subgroup   | Events                            | Total     | Events                       | Total     | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Doss 2009 (5)   | 9                                 | 279       | 12                           | 287       | 4.7%   | 0.77 [0.33, 1.80]   | <del></del>         |
| Doss 2010 (6)   | 8                                 | 239       | 10                           | 237       | 4.1%   | 0.79 [0.32, 1.98]   | <del></del>         |
| Hofman 2006 (7)   | 4                                 | 124       | 8                            | 133       | 2.5%   | 0.54 [0.17, 1.74]   | <del></del>         |
| Luger 2001 (8)  | 5                                 | 42        | 14                           | 45        | 3.9%   | 0.38 [0.15, 0.97]   |                     |
| Luger 2004 (1)  | 6                                 | 330       | 18                           | 328       | 4.1%   | 0.33 [0.13, 0.82]   | <del></del>         |
| Reitamo 2002(I) (9)   | 18                                | 186       | 29                           | 191       | 11.2%  | 0.64 [0.37, 1.11]   | <del></del>         |
| Reitamo 2002(II) (10)   | 14                                | 185       | 21                           | 186       | 8.2%   | 0.67 [0.35, 1.28]   | <del></del>         |
| Reitamo 2004 (11)   | 33                                | 207       | 45                           | 210       | 20.7%  | 0.74 [0.50, 1.12]   |                     |
| Reitamo 2005 (3)  | 65                                | 485       | 88                           | 487       | 39.3%  | 0.74 [0.55, 1.00]   | <del></del>         |
| Sikder 2005 (12)  | 2                                 | 15        | 3                            | 15        | 1.3%   | 0.67 [0.13, 3.44]   | -                   |
| Total (95% CI)  |                                   | 2092      |                              | 2119      | 100.0% | 0.68 [0.56, 0.82]   | <b>◆</b>            |
| Total events  | 164                               |           | 248                          |           |        |                     |                     |
| Heterogeneity: Tau <sup>2</sup> = 0   | 0.00; Chi <sup>2</sup> = $4.80$ , | df = 9 (P | = 0.85); I <sup>2</sup> = 0% |           |        |                     | 0.01 0.1 1 10 100   |
| Test for overall effect: Z = 4.11 (P < 0.0001)  Test for overall effect: Z = 4.11 (P < 0.0001)  More events with TCI More events with |                                   |           |                              |           |        |                     |                     |

4) Skin infections

|                                       | Corticosteroio     | (TCS)                                     | Calcineurin inhibit | tor (TCI) |        | Risk Ratio          | Risk Ratio          |
|---------------------------------------|--------------------|---|---------------------|-----------|--------|---------------------|---------------------|
| Study or Subgroup                     | Events             | Total                                     | Events              | Total     | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Doss 2010 (6)                         | 49                 | 239                                       | 44                  | 239       | 14.6%  | 1.11 [0.77, 1.60]   | <del>-</del>        |
| Hofman 2006 (7)                       | 4                  | 124                                       | 2                   | 133       | 0.7%   | 2.15 [0.40, 11.51]  | <del>-   ·</del>    |
| Luger 2004 (1)                        | 80                 | 330                                       | 69                  | 328       | 24.2%  | 1.15 [0.87, 1.53]   | <del> -</del>       |
| Mandelin 2010 (2)                     | 17                 | 40  | 26                  | 40        | 10.7%  | 0.65 [0.43, 1.00]   |                     |
| Reitamo 2002(II) (10)                 | 4                  | 185                                       | 4                   | 186       | 1.0%   | 1.01 [0.26, 3.96]   | <del></del> -       |
| Reitamo 2004 (11)                     | 6                  | 207                                       | 6                   | 210       | 1.6%   | 1.01 [0.33, 3.09]   | <del></del>         |
| Reitamo 2005 (3)                      | 9                  | 485                                       | 13                  | 487       | 2.8%   | 0.70 [0.30, 1.61]   | <del></del>         |
| Sigurgeirsson 2015 (4)                | 150                | 1213                                      | 157                 | 1205      | 44.5%  | 0.95 [0.77, 1.17]   | <del>†</del>        |
| Total (95% CI)                        |                    | 2823                                      |                     | 2828      | 100.0% | 0.98 [0.85, 1.12]   | •                   |
| Total events                          | 319                |   | 321                 |           |        |                     |                     |
| Heterogeneity: Tau <sup>2</sup> = 0.0 | 00; Chi² = 6.80, d |   | 0.01 0.1 10 100     |           |        |                     |                     |
| Test for overall effect: Z =          | 0.33 (P = 0.74)    | More events with TCL More events with TCS |                     |           |        |                     |                     |

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